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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/521,524 | 03/08/00 | DAVIDSON B | 875.025US1 |

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HM22/1116

| EXAMINER | |
|---|---|
| FOLEY,S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | 4 |

**DATE MAILED:** 11/16/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/521,524 | DAVIDSON ET AL. | |
| | Examiner | Art Unit | |
| | Shanon A. Foley | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 16, and 17-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 16, 17, and 22 recites "an adenovirus backbone plasmid comprising an Ad genome lacking map units 0-9.2, starting with the lefthand ITR". Is the ITR included in the 0-9.2 map unit that is deleted? Or does the 0-9.2 map unit deletion start immediately after the ITR? Is the ITR present or not? Claims 2-10 and 18-25 are rejected for depending on the rejected claim.

Claim 9 is drawn to HSV Ampicon sequences that are positioned on either side of the left and right ITR's. How is this possible if the lefthand ITR is missing in claims 1, 16, 17, and 22? The specification on page 6, line 15, and page 8, lines 19-20 state that the ITR is lacking, so it is confusing whether or not the ITR is present or not.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 4-6, 10, 11, 13-19, and 22-25 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Aoki et al.

The claims are drawn to an adenovirus backbone plasmid comprising an Ad genome lacking map units 0-9.2, where the E3 gene has been modified by deletion, substitution, or insertion. The plasmid further comprises sequences that allow for integration of sequences into cells after viral infection. Also claimed is a shuttle plasmid comprising Ad sequences from 0-1 and 9.2-16.1 map units of an Ad genome with a multiple cloning site between map units (mu) 1 and 9.2. The shuttle vector also comprises a promoter to drive expression of a transgene. The combination of the Ad backbone plasmid and the shuttle plasmid comprise a cloning system for serially and rapidly generating recombinant virus in an animal host cell that expresses the E1 sequences necessary for adenovirus replication.

Aoki et al. teaches a method of rapidly generating replication-defective adenoviral vectors without detectable wild-type virus, see the abstract, "recombined adenovirus DNA..., page 227-228, "time course of viral production" on page 228, and the discussion section on pages 228-230. A shuttle plasmid was constructed that contained the adenovirus 5'-ITR and a packaging signal from 0-1 mu, the transgene of interest, and a single loxP sequence 3' of the transgene and 9.2-16.1 mu. A multiple cloning site would have been anticipated to insert the transgene of interest. An adenovirus cosmid was also generated to include 9.2-100 mu of the adenovirus genome, a deletion in the E3 region and a loxP site at 9.2 mu. Cre recombinase produces the full-length recombinant adenoviral vector in vitro by intermolecular recombination between the loxP sites in these two linearized molecules. The Cre-treated DNA is transfected into adeno-viral helper cell lines such as 293 cells that are well known in the art to produce E1

necessary to aid in adenovirus replication, see the first paragraph of the results section on page 226. These teachings anticipate claims 1, 4-6, 10, 11, 13-19, and 22-25.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. as applied to claims 1, 4-6, 10, 11, 13-19, and 22-25 above, and further in view of Krougliak et al.

The claims are drawn to an adenovirus backbone plasmid where any or all reading frames of E4 have been modified by substitution, deletion, or insertion and an animal host cell that expresses E1, pIX, and E4 sequences required for the expression of viruses.

See the teachings of Aoki et al. above. Aoki et al. does not teach modification of the E4 region or a cell line that expresses E1, E4, and pIX, however, Krougliak et al. teaches the modification of E4 and the generation of a helper cell line that expresses E1, E4, and pIX.

Krougliak et al. teaches the development of cell lines expressing adenovirus type 5 E1, E4, and pIX and demonstrate that these cell lines (to see cell line clones generated, see the first paragraph of the results section on page 1578) are able to complement replication of adenovirus mutants defective in each of these regions, see the last paragraph of the first column on page 1576. The cell lines found to be successful in generating and propagating adenovirus with

deletions in E1, E3, and E4 regions were VK2-20 and VK10-9 see the paragraph bridging pages 1582 and 1583 and the last paragraph of the discussion section bridging pages 1584-1585.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the teachings of Aoki et al. if one wanted to express a large piece of foreign DNA into the an adenovirus genome, taught by Krougliak et al. Aoki et al. teaches a fast method for generating recombinant Ad viruses without contamination of the wild type virus and Krougliak et al. teaches a cell line that aids in successfully producing recombinant adenoviruses that have large sections deleted from them, see the "overview summary" on page 1575 and the first full paragraph on page 1576. Therefore the teachings of Aoki et al. and Krougliak et al. render claims 1-6, 10, 11, and 13-25 obvious to one of ordinary skill in the art at the time the invention was made.

Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al. and Krougliak et al. as applied to claims 1-6, 10, 11, and 13-25 above, and further in view of Breakfield et al. in U.S. Patent 5,965,441.

The claims are drawn to the E3 gene of an adenovirus has one or more genes required for Herpes Simplex Virus (HSV) packaging and replication and HSV Amplicon sequences are placed on either side of the Ad left and right ITRs.

See the teachings of Aoki et al. and Krougliak et al. above. Neither Aoki et al. or Krougliak et al. teach inserting HSV packaging, replication, and Amplicon sequences within the E3 region of an Ad backbone plasmid. However, Breakfield et al. teaches a hybrid vector system that incorporates elements of herpesvirus and adeno-associated virus that is capable of expressing a gene product in eukaryotic cells. The vector system taught by Breakfield et al.

provides a means of packaging plasmid DNA into highly infectious virions which can safely and efficiently deliver transgenes to both mitotic and post-mitotic cells in a state that can be maintained for long periods of time, see the abstract.

See figure 1 for the Amplicon constructs, which include transgene elements that are introduced into amplicon vector bearing the lacZ marker gene that contained the HSV-1 ori and the DNA packaging and cleaving signal, pac, which is located on either side of the adeno-associated virus (AAV) ITR, see the description of figure 1 in column 3, lines 50-65, and column 7, lines 35-38. Breakfield et al. teaches that the adenoviruses and AAV can generate long-term gene expression in post-mitotic cells, but not mitotic cells without the aid of the amplicon, see column 5, lines 26-36. The hybrid vectors taught by Breakfield et al. can deliver the transgene out of the amplicon DNA, which is stabilized through hairpin hybridization of the ITR sequences which are resistant to nuclease digestion and thus be expressed in dividing and non-dividing cells, see column 10, lines 39-67 and column 11, lines 1-10.

Although Breakfield et al. does not teach the hybrid vectors as being specifically adenovirus shuttle vectors containing HSV ori, packaging, and amplicon genes. However, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the AAV/HSV hybrid vector taught by Breakfield et al. to the fast method for generating recombinant Ad viruses without contamination of the wild type virus taught by Aoki et al. with the cell line that successfully produces recombinant adenoviruses that have large sections deleted from them taught by Krougliak et al. because one would have the desire to expand the host range of gene expression to dividing cells. One of ordinary skill in the art at the time the invention was made would have immediately recognized the analogous genomes of AAV used in the teachings

of Breakfield et al. and applied the teachings to the adenovirus shuttle vector taught by Aoki et al. Therefore, the teachings of Aoki et al., Krougliak et al., and Breakfield et al. render claims 1-11, and 13-25 obvious to one of ordinary skill in the art at the time the invention was made.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki et al., Krougliak et al., and Breakfield et al. as applied to claims 1-11 and 13-25 above, and further in view of Chartier et al.

The claim is drawn to the shuttle plasmid containing *Pac*I endonuclease sites flank either end of the Ad sequences.

See the teachings of Aoki et al., Krougliak et al., and Breakfield et al. above. Aoki et al., Krougliak et al., and Breakfield et al. do not teach the shuttle plasmid containing *Pac*I endonuclease sites flanking either end of the Ad sequences, but Chartier et al. teaches why one of ordianary skill in the art at the time the invention was made would be motivated to put the sites there.

Chartier et al. teaches the introduction of two unique *Pac*I sites that were introduced by PCR immediately upstream of the lefthand ITR and downstream of the right ITR. *Pac*I is absent in Ad5 genomic DNA and allows for the precise excision of the gene of interest, see the paragraph bridging pages 4806-4807, figure A on page 4806, figure 2 on page 4808. The identification of another unique restriction site within the adenovirus genome, in addition to *Cla*I, *Bam*HI, and *Spe*I, that can be easily cloned anywhere by PCR in the adenivirus genome without the fear of another identical site enables one of ordinary skill in the art a wider variety of choices for cloning sites in addition to the increased number of genes that can be cloned, see the paragraph bridging pages 4809-4810.

One of ordinary skill in the art at the time the invention was made would have been motivated to utilize the fast method for generating recombinant Ad viruses without contamination of the wild type virus taught by Aoki et al., a cell line that aids in successfully producing recombinant adenoviruses that have large sections deleted from them taught by Krougliak et al. with the hybrid vectors taught by Breakfield et al. that can deliver the transgene which is stabilized through hairpin hybridization of the ITR sequences which are resistant to nuclease digestion and thus be expressed in dividing and non-dividing cells with the additional unique restriction site within the adenovirus genome to enable one of ordinary skill in the art a wider choice of cloning sites within the adenovirus genome.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
November 11, 2000

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1600